Paper No. 32

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Ex parte SUSAN LINDQUIST

Appeal No. 2003-1661
Application No. 09/207,649

HEARD: February 19, 2004

Before SCHEINER, MILLS and GREEN, Administrative Patent Judges.

MILLS, Administrative Patent Judge.

DECISION ON APPEAL

This is a decision on appeal under 35 U.S.C. §134 from the examiner's final rejection of claims 1, 3, 7-20, 22 and 37, which are all of the claims pending in this application.

Claim 1 is illustrative of the claims on appeal and reads as set forth below:

1. A method for identifying a candidate substance that inhibits the aggregation of a mammalian aggregate-prone amyloid protein, comprising:
(a) contacting a yeast cell that expresses a chimeric aggregate-prone amyloid protein comprising a mammalian aggregate-prone amyloid peptide with said candidate substance under conditions effective to allow aggregated amyloid formation; and
(b) determining the ability of said candidate substance to inhibit the aggregation of the aggregate-prone amyloid protein.

The references relied upon by the examiner are:

Findeis et al. (Findeis)	5,854,204	Dec. 29, 1998
Cordell et al. (Cordell) PCT Publication	WO 91/04439	April 4, 1991

Hughes et al. (Hughes), "Two-hybrid system as a model to study the interaction of β-amyloid peptide monomers," Proc. Nat. Acad. Sci., Vol. 93, pp. 2065-2070 (1996)

Grounds of Rejection

Claims 1, 3, 7, 12, 13 and 17-18 stand rejected under 35 U.S.C. § 102(b) as anticipated by Hughes.

Claims 1, 3, 7, 12, 13, 15, 17-19 and 37 stand rejected under 35 U.S.C. § 102(b) as anticipated by Cordell.

Claims 1, 3, 7, 12, 13, 15, 17-18 and 37 stand rejected under 35 U.S.C. § 102(b) as anticipated by Findeis.

Claims 1, 3, 7-20, 22 and 37 stand rejected under 35 U.S.C. § 112, second paragraph as indefinite.

We reverse these rejections.

DISCUSSION

In reaching our decision in this appeal, we have given consideration to the appellant's specification and claims, to the applied references, and to the respective positions articulated by the appellant and the examiner.

Rather than reiterate the conflicting viewpoints advanced by the examiner and the appellant regarding the noted rejections, we make reference to the examiner's Answer for the examiner's reasoning in support of the rejection, and to the appellant's Brief for the appellant's arguments thereagainst. As a consequence of our review, we make the determinations which follow.

Background

The claimed invention is directed to a method for identifying a candidate substance that inhibits the aggregation of a mammalian aggregate-prone amyloid protein, comprising: (a) contacting a yeast cell that expresses a chimeric aggregate-prone amyloid protein comprising a mammalian aggregate-prone amyloid peptide with said candidate substance under conditions effective to allow aggregated amyloid formation; and (b) determining the ability of said candidate substance to inhibit the aggregation of the aggregate-prone amyloid protein.

In a broader sense, the invention "relates to the determination of compounds that affect the amyloid associated with Alzheimer's disease, Transmissible spongiform encephalopathies (TSE's), and several rare neuropathies: Creutzfeld-Jacob disease (CJD), fatal familial insomnia (FFI), Gertsmann-Straussler-Scheinker (GSS) syndrome, and kuru." Specification, page 2.

"A central event in TSE pathogenesis is the accumulation in the nervous system of an abnormally-folded version (PrP^{Sc}) of a normal cellular protein, (PrP^{C})." It has

been observed that "[t]he chaperone protein Hsp 104 controls the genetic behavior of a mysterious yeast prion-like element known as [PSI+]. The chaperone Hsp104 controls the aggregation of Sup35, the protein determinant of [PSI+]." "The protein Sup35 forms amyloid-like protein fibers *in vitro*. This is a property shared by other amyloidogenic proteins that cause human disease." Specification, page 4. The yeast protein Hsp104 affects the behavior of Sup35 *in vitro*. Specification, page 5. When mammalian PrP is expressed in yeast cells, its folding state depends upon the Hsp104 protein. According to the specification, it is this element that establishes that yeast can provide an excellent model for studying factors that affect the folding properties of human disease proteins that have an amyloidogenic character. Id.

Further according the specification, page 5, the term "aggregate-prone amyloid protein" is meant to be any protein that is able to form an amyloid or amyloid like deposit. Amyloid or amyloid-like deposits are generally insoluble fibrillary material. Although many proteins are capable of aggregating at high concentrations, aggregate prone amyloid proteins are able to, and often do, aggregate under physiological conditions, such as inside of a cell. Aggregate-prone amyloid proteins include yeast proteins such as Sup35 and URE3, and mammalian proteins, such as PrP and β-amyloid polypeptide. Id.

35 U.S.C. § 102(b)

Claims 1, 2, 8, 11, 15, 16, 22 and 23 stand rejected under 35 U.S.C. § 102(b) as anticipated by Hughes.

"A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." Verdegaal Bros., Inc. v. Union Oil Co., 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). "It is also an elementary principle of patent law that when, as by a recitation of ranges or otherwise, a claim covers several compositions, the claim is 'anticipated' if one of them is in the prior art." Titanium Metals Corp. of America v. Banner, 778 F.2d 775, 782, 227 USPQ 773, 779 (Fed. Cir. 1985).

According to the examiner, Hughes teaches a "yeast-two hybrid system as a method of identifying amyloid aggregation and aggregating domains which are capable of inhibiting amyloid aggregation... Hughes identifies candidate substances (mutated forms of amyloid or alternate proteins) which inhibit the self-aggregation of amyloid peptides. Hughes explains that the kinetics of amyloid fibril formation by beta-amyloid is typical of a nucleation-dependent polymerization mechanism." Answer, pages 4-5.

More specifically, the examiner finds claim 3 is anticipated by Hughes et al. as the aggregate-prone protein comprises -amyloid chimeric proteins (LexA-A fusion and B42-A fusion). Id., at 5. According to the examiner, claim 7 is anticipated as the chimeric fusion protein comprises at least an aggregate forming domain and defines at least residues 19 and 20 as a domain critical to such aggregate formation of

mammalian amyloid polypeptide, operably attached to a detectable marker protein. A marker protein is the bait and prey construct which leads to the expression of reporter plasmids LEU2 and lacZ genes. Claims 12-13 are indicated by the examiner to be anticipated by Hughes as the amyloid polypeptide is -amyloid and comprises at least about 1-42 amino acids. Claims 17-18 are anticipated because the aggregate is labeled with a chromophore (ECL detection). Answer, page 5.

If the PTO establishes a prima facie case of anticipation, the burden shifts to the appellants to prove that the subject matter shown to be in the prior art does not possess the characteristics of the claimed invention. See In re Thorpe, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985); In re King, 801 F.2d 1324, 1327, 231 USPQ 136, 138 (Fed. Cir. 1986).

Appellant responds, arguing that "Hughes et al describes a typical use of a yeast two-hybrid system....this reference precisely shows that the system can evaluate the ability of ***only*** monomers to associate." Brief, page 10. Hughes also states that "[r]esults presented in Fig. 4. also suggest that no covalent higher order bait-prey aggregates can be observed on the gel. This system may therefore provide an opportunity to freeze-frame the monomer-monomer interaction." Hughes, page 2070, column 1; Brief, page 11.

Appellant argues that the yeast two-hybrid system of Hughes is limited to proteins that can be localized to the nucleus, which may prevent its use with certain extracellular proteins. "In the assays of the present invention, aggregation prevents the

polypeptides from reaching the nucleus." Brief, page 12. Appellant concludes that the "yeast-two hybrid system is simply inoperable for the intended purpose of the assay if practiced according to the limitations of the claimed invention." Id. In other words, Hughes does not teach an aggregation step, i.e., Hughes does not teach a step of contacting a yeast cell that expresses a chimeric aggregate-prone amyloid protein comprising a mammalian aggregate-prone amyloid peptide with said candidate substance under conditions effective to allow aggregated amyloid formation. Hughes only teaches the coming together of two monomers.

The examiner replies, arguing, "[c]onsistent with Hughes, the interaction of monomers is hypothesized as being the nucleation event and thus it is apparent from the art that aggregation begins with the formation of two monomers." Answer, page 13. The examiner argues (Answer, page 14) that "there is no limitation in the claims that requires greater than two monomeric forms." We disagree. We find a distinction between the coalescing of two monomeric protein forms and the formation of an aggregate as required by the claims. We do not find the examiner has addressed appellant's argument that the assay of Hughes does not and cannot measure amyloid aggregation.

We agree with the appellant that Hughes, in its failure to teach a step of contacting a yeast cell that expresses a chimeric aggregate-prone amyloid protein comprising a mammalian aggregate-prone amyloid peptide with a candidate substance under conditions effective to allow aggregated amyloid formation, fails to teach each

and every element of the method of the claimed invention.

The examiner has failed to establish a prima facie case of anticipation in view of Hughes. The rejection of the claims for anticipation by Hughes is reversed.

35 U.S.C. § 102(b)

Claims 1, 3, 7, 12, 13, 15 and 17-19 and 37 stand rejected under 35 U.S.C. § 102(b) as anticipated by Cordell.

Cordell, as found by the examiner, teaches assays and reagents for amyloid deposition including the identification of agents which inhibit amyloid formation. According to Cordell, the amyloid products may be expressed in yeast and include beta-amyloid 1-42 and preamyloid precursors. The methods include screening compounds for inhibition of aggregate formation and the amyloid aggregates are detected by Congo red. Answer, page 6.

Appellant argues that Cordell does not teach a "chimeric aggregate prone amyloid protein." Brief, page 13. Appellant particularly argues that, "[i]t is well known to people skilled in the art that a chimeric protein contains at least two separate polypeptides combined into one whole protein." Id. Appellant argues that their definition of "chimeric protein" does not include polypeptides with substitutions of single amino acids. Brief, pages 13-14. Thus, appellant argues that Cordell does not teach each and every element of the claimed invention. Brief, page 14.

The examiner responds, arguing that the amyloid peptides of Cordell encompass "various mutations including of N and C' terminally modified sequences." Answer, pages 14-15. The examiner continues, "Appellant's specification defines ... a chimeric protein to mean that the protein comprises polypeptides that do not naturally occur together in a single protein unit." Answer, page 14.

To some extent we agree with the examiner that Cordell discloses a chimeric protein within the scope of appellant's claims. In particular, appellant indicates on page 6 of the specification that the "chimeric protein comprises at least an aggregate forming domain of an aggregate-prone amyloid protein operably attached to a detectable marker protein." Figure 1 of Cordell depicts a plasmid including 42 aa amyloid protein and a marker protein such as from a gene for ampicillin resistance. Cordell, page 10. This plasmid can be inserted into a prokaryotic, eukaryotic, yeast or mammalian cell. Cordell, pages 7, 10-11, 16.

We disagree with the examiner that the disclosure of Cordell rises to the level of an anticipatory reference. It would appear that Cordell does not provide a literal example of an assay which uses a yeast host cell and is conducted to determine the ability of said candidate substance to inhibit the aggregation of the aggregate-prone amyloid protein. While Cordell generally suggests that its culture assay may be used to test for putative therapeutic agents and to screen potential amyloid intervening agents (Cordell, pages 4-5), Cordell also discloses immunological diagnostic reagents for Alzheimer's disease. Thus, an apparent amount of selection of portions of the

disclosure of Cordell on the part of one of ordinary skill in the art is involved to arrive at the claimed invention. In view of the above, the rejection of the claims for anticipation by Cordell is reversed.[1]

35 U.S.C. § 102(e)

Claims 1, 3, 7, 12, 13, 15 and 17-18 and 37 stand rejected under 35 U.S.C. § 102(e) as anticipated by Findeis.

Findeis teach A-beta peptides including chimeric peptides as defined in the specification which differ from naturally occurring beta amyloid at one or more amino acid residues and include aggregating domains which aggregate portions of beta amyloid. Findeis also teach screening assays using such peptides to identify modulatory influences on amyloid aggregation. The peptides are expressed in S. cerevisiae. The peptides may also be fusion proteins or chimeras and may be detected by biotinylation, labeled by fluorescence, or monitored in seeded assays.

Appellant argues that the rejection in view of Findeis must fail as Findeis does not teach or suggest incubating yeast cells "under conditions effective to allow aggregated amyloid formation." Brief, page 16.

The examiner responds, arguing, that "Findeis does teach expression of the peptide modulators via recombinant technology in yeast, see in particular col. 38, lines 5, 12 and 60-65." Answer, page 15.

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[1] See Other Issue Below.

We agree with appellant that the act of expressing peptide modulators via recombinant technology in yeast is not the same as contacting an intact yeast cell that expresses a chimeric aggregate-prone amyloid protein comprising a mammalian aggregate-prone amyloid peptide with a candidate substance under conditions effective to allow aggregated amyloid formation, as claimed. For this reason, we do not find that Findeis discloses each and every element of the claimed method.

The rejection of the claims for anticipation by Findeis is reversed.

35 U.S.C. § 112, second paragraph

Claims 1-7, 9-16 and 25 stand rejected under 35 U.S.C. § 112, second paragraph as indefinite.

The examiner argues that the terms "-amyloid", and "-amyloid protein" are indefinite because the recitations are not the same and the artisan cannot discern the difference between the scope of the terms. As there are multiple "amyloid" peptides of various sequences and lengths recognized in the art, and the terms are not defined in the specification, the artisan cannot discern the metes and bounds or difference in scope of the various recitations. Answer, page 7.

One of the purposes of 35 U.S.C. § 112, second paragraph, "is to provide those who would endeavor, in future enterprise, to approach the area circumscribed by the claims of a patent, with adequate notice demanded by due process of law, so that they may more readily and accurately determine the boundaries of protection involved and

evaluate the possibility of infringement and dominance." In re Hammack, 427 F.2d 1378, 1382, 166 USPQ 204, 208 (CCPA 1970) (citations omitted). As set forth in Amgen Inc. v. Chugai Pharmaceutical Co., Ltd., 927 F.2d 1200, 1217, 18 USPQ2d 1016, 1030 (Fed. Cir. 1991):

> The statute requires that "[t]he specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention." A decision as to whether a claim is invalid under this provision requires a determination whether those skilled in the art would understand what is claimed. See Shatterproof Glass Corp. v. Libbey-Owens Ford Co., 758 F.2d 613, 624, 225 USPQ 634, 641 (Fed. Cir. 1985) (Claims must "reasonably apprise those skilled in the art" as to their scope and be "as precise as the subject matter permits.").

Furthermore, claim language must be analyzed "not in a vacuum, but always in light of the teachings of the prior art and of the particular application disclosure as it would be interpreted by one possessing the ordinary skill in the pertinent art." In re Moore, 439 F.2d 1232, 1235, 169 USPQ 236, 238 (CCPA 1971).

We do not agree with the examiner that the claim language is indefinite, i.e., that a person skilled in the art would not understand the bounds of the claims when read in light of the specification. See Miles Laboratories Inc. v. Shandon Inc., 997 F.2d 870, 875, 27 USPQ2d 1123, 1126 (Fed. Cir. 1993). In fact, the examiner's arguments would appear to indicate that the examiner is not concerned merely with the specific meaning of the claim language but the breadth or broad scope of the claim language. However, breadth of a claim is not to be equated with indefiniteness. See In re Miller, 441 F.2d 689, 169 USPQ 597 (CCPA 1971). The rejection under 35 U.S.C. § 112, second

paragraph, is reversed.

Other Issue

Upon return of the application to the examiner, the examiner is encouraged to take a step back and review the disclosure of the Cordell reference. In view of the discussion above regarding the Cordell reference, the examiner should determine whether the disclosure of Cordell would render obvious the claimed method, alone or in combination with an appropriate secondary reference. If appropriate, the examiner should enter a rejection of the claims for obviousness under 35 U.S.C. § 103.

CONCLUSION

The rejections of claims 1, 3, 7, 12, 13 and 17-18 under 35 U.S.C. § 102(b) as anticipated by Hughes; claims 1, 3, 7, 12, 13, 15 and 17-19 and 37 under 35 U.S.C. § 102(b) as anticipated by Cordell; claims 1, 3, 7, 12, 13, 15 and 17-18 and 37 under 35 U.S.C. § 102(b) as anticipated by Findeis and claims 1, 3 7-20, 22 and 37 under 35 U.S.C. § 112, second paragraph as indefinite are reversed. The examiner should review the application with respect to the "other issue" noted by the Board.

No time period for taking any subsequent action in connection with this appeal may be extended under 37 CFR § 1.136(a).

REVERSED

TONI R. SCHEINER
Administrative Patent Judge

DEMETRA J. MILLS
Administrative Patent Judge

LORA M. GREEN
Administrative Patent Judge

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) INTERFERENCES

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